Remarks

Claims 1-27 are pending in this application; claims 15-23 are currently withdrawn from examination. Reconsideration of the outstanding Office action is respectfully requested.

I. Interview

Applicants appreciate the Examiner's courtesy in granting Applicants a telephone interview on March 11, 2004. Claims 1-14 and 24-27 and the references Weckwerth, Gygi, and Aebersold were discussed. Applicants' representatives noted concern that the Office action does not set forth a *prima facie* case of obviousness because there is no motivation to combine the cited references. No agreement was reached, but Applicants believe that this response should resolve the remaining issues and place the application in condition for allowance.

II. 35 U.S.C. § 103(a) Rejections

The Office action repeats the rejections set forth in the Office action of July 1, 2003, rejecting claims 1-14 and 24-27 as allegedly being obvious over Weckwerth et al., when taken in combination with Gygi et al., or Aebersold et al. Applicants traverse these rejections.

A. Claims 1-13 Are Nonobvious

Below Applicants address the Examiner's concern regarding "presynthesized" reagents, discuss the lack of the required motivation to combine the cited references and how the cited art teaches away from Applicants' method, and further set forth objective evidence indicating that Applicants' method is nonobvious.

1. Modifying Weckwerth's Disclosed Method to Use a "Presynthesized" Reagent as Disclosed in Aebersold or Gygi Does not Result in a Method with all the Features of Applicants' Claimed Method

The current Office action states that the rationale for combining the cited references is "set forth in the second full paragraph of page 3 of the July 01, 2003 Office action." (1/28/04 Office action, 3.) That earlier Office action stated,

> In view of the fact that "presynthesized" labeled ICAT reagents are well known in the art . . . (Gygi et al and Aebersold et al), it would have been obvious to modify the multi-step method of Weckwerth et al by employing a "presynthesized" reagent as described by Gygi et al or Aebersold et al. (7/1/03 Office action, 3.)

Applicants note that the term "presynthesized" is not recited in Applicants' claims. The obviousness or nonobviousness of a feature not recited in Applicant's claims has no bearing on whether Applicants' claimed method is obvious or is not obvious.

Moreover, Weckwerth discloses only the addition of an ethanethiol to a peptide residue subsequent to beta-elimination of phosphate. Weckwerth does not disclose a method comprising providing a protein reactive reagent including a binding agent (B), as is recited in claim 1. Thus, even if the reagent used in Weckwerth's disclosed method was modified to be a presynthesized reagent (as in Aebersold or Gygi) Weckwerth still would not disclose the use of a protein reactive reagent satisfying Applicants' recited formula B-L-PhRG, because there would be no binding agent.

As stated in the MPEP, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2142. Because the combination asserted in the Office action does not disclose all the features of Applicants' recited protein reactive reagent the asserted combination does not set forth a *prima facie* case of obviousness.

2. No Motivation to Combine the Disclosure of Weckwerth with the Disclosures of Aebersold and Gygi has Been Demonstrated

Even if, arguendo, one were to agree that the combination of Weckwerth, Aebersold and Gygi discloses all the features of Applicants' claimed methods, there is no motivation to combine the references to perform Applicants' claimed methods.

The MPEP states that "when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to: . . . (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination." MPEP § 2141.01. Where, as here, the cited references do not "expressly or impliedly suggest the claimed invention ... the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious." MPEP § 2142.

The irrelevance of the rationale for combining the cited references set forth in the Office action (i.e., that a "presynthesized" reagent is an obvious modification of Weckwerth in view of Aebersold and Gygi) has already been discussed. The Office action does not set forth any additional rationales for the proposed combination. Thus, the Office action has not demonstrated the necessary motivation to combine the cited references.

Moreover, even assuming solely for the sake of argument that physically combining the affinity tags disclosed in Aebersold/Gygi with Weckwerth's disclosed reagent would result in the protein reactive reagent recited in Applicants' claimed method, Applicants' claimed method of using Applicants' recited protein reactive reagent still would not be obvious. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP 2143.01 (first emphasis in original, second added). Even where "the references relied upon teach that all the aspects of the claimed invention were individually known in the art [it] is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references." MPEP 2143.01. In this case, the art of record does not set forth any desirability of the combination of Weckwerth with Aebersold/Gygi. In fact, the art argues against such a combination, as discussed below.

3. The Primary Reference in the Office Action, Weckwerth, Teaches Away From Combining Its Disclosure with Aebersold and Gygi

Not only is there no motivation to combine the cited references, but the Examiner's primary reference teaches away from such a combination. The MPEP states that "[i]t is improper to combine references where the references teach away from their combination." MPEP § 2145 D. Weckwerth teaches away from the use of isotope coded affinity tag (ICAT) techniques using reagents having affinity tags (e.g., biotin), such as those disclosed in Aebersold and Gygi. In particular, Weckwerth states,

> Current ICAT methods use chemical attachment of biotin groups to cysteine peptide residues. Therefore peptides bearing post translational modifications will be lost during biotin/avidin affinity purification. Among these, reversible protein phosphorylation at the hydroxyl group of serine, theonine, or tyrosine is regarded as one of the major

regulatory mechanisms for controlling the intracellular protein functionality. (Weckwerth, 1677.)

By suggesting the disadvantages of the affinity tag techniques disclosed in Aebersold and Gygi, Weckwerth teaches away from modifying his disclosed method by using a reagent having Applicants' recited binding agent. Weckwerth's teaching away is also evidenced by the fact that after discussing the disadvantages of Aebersold/Gygi's affinity tag method, Weckwerth presents a new method that does not include the use of a reagent having an affinity tag. A reference discussing the disadvantages of features in a prior method and omitting such features of the prior method in a new method would suggest to one of ordinary skill in the art that the features of the prior method and the new method should not be combined. Even if this excerpted portion of Weckwerth is short relative to the entire disclosure (as mentioned by the Examiner), "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP 2141.02 (emphasis in original).

Moreover, Weckwerth was aware of Aebersold and Gygi's work, yet still did not teach or suggest a method comprising providing Applicants' claimed protein reactive reagent. (See Weckwerth, 1677) (stating, "Recently, quantifying relative protein expression levels has been achieved by Aebersold et al using a combination of chemical stable isotope labeling in vitro and affinity purification" and citing, in footnote two, the Gygi publication cited in this case).) No such teaching or suggestion was made by Weckwerth despite the fact that Weckwerth's paper disclosed a method in the same field as Applicants' recited method. Weckwerth's failure to disclose Applicant's invention under these circumstances is consistent with Weckwerth's teaching away from Applicants' claimed method and also is highly probative evidence suggesting that a person of ordinary skill in the art would not have found Applicants' claimed method obvious.

4. Objective Evidence Strongly Suggest that Applicants' Claimed Method Is Nonobvious

Objective evidence strongly supports the fact that Applicants' method is nonobvious. In particular, those in Applicants' field, including the author of one of the publications relied on in the

Office action, have praised Applicants claimed method as "creative," "clever," and a "landmark discovery," as shown in the examples discussed below.

Courts have held that praise from those in the field is an objective indicium of nonobviousness that must be considered. For example, the Federal Circuit (whose decisions are binding on the Patent Office) in one case found litigated claims nonobvious in part because the infringer "cop[ied] the invention and prais[ed] the advantages in its catalogs." Allen Archery, Inc. v. Browning Mfg. Co., 819 F.2d 1087, 1092 (Fed. Cir. 1987) (emphasis added). Another court identified "praise of the invention by those in the field" as one of "nine objective factors" of nonobviousness. Pechiney Rhenalu v. Alcoa Inc., 224 F. Supp. 2d 773, 800 (D. Del. 2002) (emphasis added).

As an example of the praise Applicants' invention has received, Aebersold (the first inventor named on the cited "Aebersold" reference) cited one of Applicants' papers in Analytical Chemistry concerning Applicants' invention as an example of "proteomics technologies . . . being used in **creative** experiments to measure biologically informative properties of the proteome." Tao and Aebersold, Advances in quantitative proteomics via stable isotope tagging and mass spectroscopy, *Current Opinion in Biotech.*, 14:110-118, 113 (2003) (emphasis added) (attached as Exhibit A) (citing Applicants' paper, Goshe et al., Phosphoprotein isotope-coded affinity tags: application to the enrichment and identification of low-abundance phosphoproteins, *Anal. Chem.*, 74:607-616 (2002) (attached as Exhibit B)). The fact that an author of a secondary reference relied on in the Office action stated that Applicants' claimed method was creative strongly suggests that Applicants claimed method was not obvious in view of that author's previous work.

As another example, in a paper by Witzmann & Li, Applicants' method was referred to as "**clever**." Witzmann & Li, Cutting-Edge Technology II. Proteomics: core technologies and applications in physiology, Am. J. Physiol. Gastrointest. Liver Physiol., 282:G735-741 (2002) (emphasis added) (attached as Exhibit C) (citing Applicants' paper, Goshe et al., Phosphoprotein isotope-coded affinity tag approach for isolating and quantitating phosphopeptides in proteome-wide analysis, *Anal. Chem.*, 73:2578-2586 (2001) (attached as Exhibit D)). A "clever" technique is not obvious.

In a final example of the praise Applicants' invention has received, Dr. Goshe, a primary inventor, was selected as the 2001 recipient of the M.T. Thomas Award for Outstanding Postdoctoral Achievement based on the very method claimed in Applicants' application. He was selected

"specifically for his **landmark discovery** known as the phosphoprotein isotope-coded affinity tag (PhIAT) methodology." EMSL, *M.T. Thomas Award 2001*, (last modified January 26, 2004) <http://www.emsl.pnl.gov/new/mt_thomas_award/goshe.shtml> (emphasis added) (from the website of the William R. Wiley Environmental Molecular Sciences Laboratory, a U.S. Department of Energy national scientific user facility operated by Pacific Northwest National Laboratory (PNNL)) (attached as Exhibit E).

In sum, not only has there been no demonstration of a motivation to combine Weckwerth with Gygi or Aebersold, but the art cited in the Office action teaches away from such a combination. In addition, Applicants' invention has been praised by those in the field as "creative," "clever," and a "landmark discovery." Accordingly, the Office action has not shown that claim 1 is obvious; thus, claim 1 is allowable. Claims 2-13 are allowable at least because they depend from allowable claim 1 and because of each claim's unique and nonobvious combination of features.

Accordingly, Applicants request that the Examiner withdraw the § 103(a) rejections of claims 1-13.

B. Claim 14 Is Nonobvious

Neither the outstanding Office action nor the previous Office action directly discuss whether independent claim 14 is allegedly obvious over Weckwerth in view of Aebersold/Gygi.

Independent claim 14 recites a method for screening for a therapeutic agent that alters the phosphorylation state of a protein that comprises, in part, use of a protein reactive reagent satisfying the formula B-L-PhRG. The Office actions cite no publications that teach or suggest using Applicants' recited protein reactive reagent in a method of screening for phosphorylation altering therapeutic agents.

To find a claim obvious "[t]he prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. Here, all the claim limitations are not taught. For at least this reason (as well as those discussed above in relation to claim 1) claim 14 is patentable over the art of record.

Accordingly, Applicants request that the Examiner withdraw the § 103(a) rejection of claim 14.

C. Claims 24-27 Are Nonobvious

Neither the outstanding Office action nor the previous Office action directly discuss whether independent claim 24 is allegedly obvious over Weckwerth in view of Aebersold/Gygi.

Independent claim 24 recites a method of detecting more than one type of phosphorylated amino acid residue in a protein comprising, in part, removing the phosphate group from at least one serine residue or at least one threonine residue, and removing the phosphate group from at least one tyrosine residue, and tagging the at least on serine residue or at least one threonine residue and the least one tyrosine residue with a protein reactive reagent satisfying the formula B-L-PhRG.

None of the cited references, whether considered individually or in combination, teach or suggest removing a phosphate group from a tyrosine residue and tagging the formerly phosphorylated residue with any group. Weckwerth is the only publication of the three that even discloses phosphate removal from any protein, but Weckwerth only discloses removing a phosphate group from casein, serine, and threonine residues. Weckwerth does not disclose dephosphorylation of tyrosine. "[T]he prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. Here, all the claim limitations are not taught. For at least this reason (as well as those discussed above in relation to claim 1) claim 24 is patentable over the art of record.

Claims 25-27 also are allowable at least because they depend from allowable claim 24 and also because of each claim's recitation of unique and nonobvious combinations of features.

Accordingly, Applicants request the Examiner withdraw the § 103(a) rejections of claims 24-27.

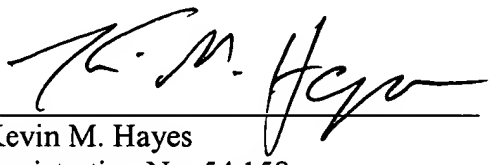
III. Conclusion

For at least the foregoing reasons, all of Applicants pending claims are allowable and Applicants respectfully request notice of the same.

If the Examiner has any further concerns, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 

Kevin M. Hayes
Registration No. 54,158

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 226-7391
Facsimile: (503) 228-9446